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EXAMINER

SCHNIZER, RICHARD A

ART UNIT PAPER NUMBER

1635

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Please find below and/or attached an Office communication concerning this application or proceeding.

DETAILED ACTION

An amendment was received and entered on 6/29/06. Claims 1-27 are pending and under consideration in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-22 have been amended to require that the recited mixing step "does not require vortexing". Applicant has not pointed to any passage of the specification to support this limitation, and none is readily apparent. While the specification as filed indicates at page 13 that the method of Evans requires vortexing, the specification provides no support for the instant limitation "does not require vortexing". In fact, the passage at page 13 seems to be intended to differentiate between the instant method and that of Evans only in terms of the number of heating and cooling steps, stating that the instant method contains "no requirement for raising the mixture to a temperature above the cloud point or multiple heating and cooling steps." However, note that instant

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claims 4, 5, and 14-17 *do* have such a requirement. In any case, the specification as filed does not adequately support the limitation "does not require vortexing", and so it represents new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-8 and 10-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al (WO 02/00844) in view of Hunter et al (US Patent 5,811,088).

As disclosed in the instant specification, Evans taught methods of formulating DNA vaccines by mixing a cationic surfactant such as benzalkonium chloride (BAK), a polyoxypropylene (POP)-polyoxyethylene (POE) copolymer such as CRL 1005, and a polynucleotide at a temperature below the cloud point of the copolymer (about 2-7°C), repeatedly cycling the temperature of the mixture above and below the cloud point of the copolymer. See paragraph bridging pages 32 and 33. The concentration ranges of nucleic acid, copolymer, and cationic surfactant are preferably in the ranges of 0.5-7.5 mg/ml, 1-70 mg/ml, and 0.1-10 mM, respectively (see page 21, line 32 to page 22, line 8.

Evans did not teach that the upper limit of the "above cloud point" temperature range should be 35°C, but MPEP 2144.05 indicates that where the claimed ranges overlap or lie inside ranges disclosed by the prior art a *prima facie* case of obviousness exists, and that generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical.

Evans also did not teach cold filtration of the formulation at any step in the process. However, it would have been obvious to one of ordinary skill in the art at the time of the invention that the formulations of Evans, intended for use as vaccines, should be sterile. Hunter taught that solutions comprising poloxamers can be sterilized by passage through a 0.22 micron filter at a cold temperature at which they are soluble. See column 18, lines 40-45. Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to cold filter formulations containing poloxamers at a temperature at which they are soluble, i.e. below their cloud point. As to the point in the method of Evans at which filtration would occur, it would clearly save time and materials to sterilize the nucleic acid, copolymer, and cationic surfactant after they had been mixed, rather than separately and individually prior to mixing. So filtration of the mixture is considered obvious to one of ordinary skill in the art at the time of the invention. Also, the mere rearrangement of steps would be *prima facie* obvious unless it can be shown that the rearrangement results in new or unexpected results (see MPEP 2144.04 (IV(C))). Thus the invention as a whole was *prima facie* obvious.

Claim 9 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al (WO 02/00844), and Hunter et al (US Patent 5,811,088) as applied to claims 1-8 and 11-22 above, and further in view of Emanuele et al (US Patent 6,933,286).

The teachings of Evans and Hunter are set forth above and render obvious methods of formulating nucleic acids with POP-POE copolymers and cationic surfactants, and sterilizing the mixtures by cold filtration. In addition to the use of POE-POP-POE copolymers such as CRL 1005, Evans also taught the use of PLURONIC R copolymers, which have the general organization POP-POE-POP required by instant claim 9. See page 22, line 20 or Evans.

Evans did not teach a POP-POE-POP copolymer wherein POP accounted for up to 20 kDa of the mass of the copolymer, and POE represented between 1 and 50% of the copolymer by weight.

Emanuele taught formulations comprising POP-POE-POP copolymers and nucleic acids for delivery to animals. The POP portion accounted for up to 20 kDa of the mass of the copolymer and the POE portion represented from 1-90% of the copolymer by weight. In one embodiment POP was 2500 Da and POE was 10% of the copolymer mass. See the claims especially claims 1-5 and 8-12.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the copolymer of Emanuele in the method of Evans as modified by Hunter. One would have been motivated to do so because Evans suggested the use of POP-POE-POP copolymers, and Martin taught that when making nucleic acid/POP-

POE-POP copolymer complexes for in vivo delivery one should use copolymers wherein POP accounted for up to 20 kDa of the mass of the copolymer and POE represented from 1-90% of the copolymer by weight. Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 6/29/06 have been fully considered but they are not persuasive.

Applicant addresses the rejections at pages 8-10 of the response. Applicant asserts that Evans exemplified vortexing after every thermal cycle, and did not suggest any other technique of mixing. Applicant then concludes that one of ordinary skill in the art having read Evans would conclude that vortexing was required to achieve the desired particles. This is unpersuasive. Although Evans exemplifies vortexing, there is no requirement for vortexing in the disclosure of Evans, and one of ordinary skill in the art could substitute for vortexing any mixing technique, such as stirring, as a matter of design choice. Applicant has presented no evidence or logic as to why one of ordinary skill in the art could not have substituted any art-recognized mixing technique for vortexing. On the other hand, at page 10, lines 1-3 of the response Applicant states that "it was well known that polynucleotide molecules may undergo undesirable fragmentation with vortexing." This is a clear admission that there was motivation to one of ordinary skill in the art to optimize the mixing means used in the method of Evans. Applicant's assertion of surprising and significant advantages is unfounded in

view of the fact that one of ordinary skill appreciated the effects on DNA topology of various mixing techniques prior to the time of the invention.

For these reasons the rejections are maintained.

Conclusion

Claims 23-27 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the

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hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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A handwritten signature in black ink, appearing to read 'Richard Schnizer', with a stylized flourish extending from the end.

Richard Schnizer, Ph.D.
Primary Examiner
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